IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appl. No.	: 10/517,338
Applicant	: WARNAAR et al
Filed	: December 9, 2004
TC/A.U.	: 1642
Examiner	: Catherine Joyce
Docket No.	: 2923-672
Customer No.	: 6449
Confirmation No.	: 2944

RULE 1.132 DECLARATION

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

We, Stefan Ullrich and Sven Warnaar, declare as follows:

1. That, Stefan Ullrich and Sven Warnaar are co-inventors of the subject matter described and claimed in the United States Patent Application Serial No. 10/517,338, filed on December 9, 2004, entitled "Co-administration of CG250 and IL-2 or IFN-α for Treating Cancer Such As Renal Cell Carcinomas".

2. That, Stefan Ullrich and Sven Warnaar are co-authors of an article entitled "A Phase II Trial with Monoclonal Antibody WX-250 in Advanced Renal Cell Carcinoma", *European Urology Supplements*, vol. 1, No. 1, January 2002, page 112. This document is, and has been, referred to as "the Bluemer document" or "Bluemer" during the course of prosecution of United States Patent Application Serial No. 10/517,338.

3. That, Stefan Ullrich and Sven Warnaar are co-inventors of the subject matter disclosed in this publication and co-inventors of the subject matter disclosed and claimed in the present application.

4. That the above publication entitled "A Phase II Trial with Monoclonal Antibody WX-250 in Advanced Renal Cell Carcinoma" refers to a monotherapy without the co-administration of any other drug or compound.

5. That a skilled artisan would recognize the above publication entitled "A Phase II Trial with Monoclonal Antibody WX-250 in Advanced Renal Cell Carcinoma" as teaching a treatment of renal cell carcinoma with the G250 antibody as a "second-line" treatment, meaning that the group of 22 patients who received a first treatment of either interferon-α or interleukin-2 were progressive afterwards because the treatment of renal cell carcinoma with either interferon-α or interleukin-2 was found to not be efficacious. Otherwise, the patients would not have needed a further, and different, treatment.

6. That, the claims of United States Patent Application Serial No. 10/517,338 are drawn to a co-administration of an antitumor antibody (e.g. G250) and interferon (e.g. interferon-α). That this co-administration of G250 and interferon-α leads to an increased efficacy in the treatment of renal cell carcinoma as compared to administration of either G250 or interferon-α alone along with a reduction in side effects. The increased efficacy is due to a synergistic effect from the co-administration of the anti-tumor antibody and an interferon. This synergistic effect could not have been predicted from the disclosure in Bluemer which discloses only a monotherapy.

7. That data regarding the increased has been presented at: 1) the UAU Meeting that took place in Anaheim, California from May 19, 2007 to May 23, 2007; 2) the ASCO meeting that took place in Chicago, Illinois from June 1, 2007 to June 5, 2007; and 3) the UCS meeting that took place on October 12-23, 2007. This data is included in Appendix A.

8. That the data shows that a combination therapy of G250 and IFN-α has increased efficacy as compared to a G250 monotherapy as disclosed in Bluemer.

9. The undersigned further declares that all statements made herein of his own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

by 

Stefan Ullrich Date

Sven Warnaar Date

145924

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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12 Feb 2009

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12 Feb 2007

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by

Stefan Ullrich Date

Sven Wamaar Date 12-02-2008

145924

AUA Meeting on 19-23 May 07 in Anaheim

UPDATE OF SURVIVAL DATA FOR TWO PHASE II STUDIES WITH MONOCLONAL ANTIBODY CG250 (RENCAREX®*) IN COMBINATION WITH IL-2 OR IFNα-2A IN METASTATIC RENAL CELL CARCINOMA PATIENTS

N. Neville[1], P. Kloepfer[1], P. Bevan[1], C. Mala[1], J Beck[2] , R. Hofmann[3], M. Kindler[4], P. Mulders[5] , M. Siebels[6], R. Oberneder[7]

[1] Wilex AG, Munich, Germany
[2] Department of Hematology/Oncolog, Johannes-Gutenberg-Universität Mainz, Germany
[3] Department of Urology, Philipps-University-Marburg, Germany
[4] Onkologische Schwerpunktpraxis, Berlin, Germany
[5] Department of Urology, University Medical, Center Nijmegen, Netherlands
[6] Department of Urology, Klinikum Großhadern, Ludwig-Maximillians-University, Munich, Germany
[7] Department of Urology, Klinikum Großhadern, Ludwig-Maximillians-University, Munich, Germany

Background:
cG250 is a chimeric monoclonal antibody of the IgG1 subtype that binds to the cell surface antigen of carboxyanhydrase IX/MN antigen found on 95% of clear cell Renal Cell Cancer Cells (ccRCC) cells but not on normal kidney tissue.
Two multi-center, open-label, prospective, single-arm phase I/II trials have been performed. cG250 was combined with low dose (LD) Interleukin 2 (IL-2) or with LD interferon (IFN) α-2a evaluating the safety and efficacy in patients with metastatic ccRCC.
This abstract provides updated survival and clinical data of these combination studies with cG250.

Methods:
Patients with stage IV ccRCC, nephrectomized for the primary tumor, and in progression at study entry were included in the study. In both trials cG250 was administered intravenously weekly from week 2 to 12. In addition, patients were treated with low dose cytokine treatment from week 1 to 12. At week 16 patients evaluated for clinical response were stratified into 2 groups: a) clinical responders into the extended treatment group to receive treatment for an additional 6 weeks, or b) clinical non-responders into the discontinued group.

Results:
In the combination study with IL-2 35 patients were treated. One out of 30 evaluable patients showed partial remission for at least 8 months. 11 patients had stable disease in week 16; of which 6 patients had durable stable disease of 24 weeks or longer. Clinical benefit, defined as the sum of complete or partial responses and patients with stable disease of ≥ 24 weeks, was obtained in 23% (7/30) patients. Newest data showed a median overall survival of 22 months and a 2 year survival of 45%. Patients receiving extended treatment showed a longer 2 year survival rate than discontinued patients (55% vs. 25%; p=0.0062)
For the IFN combination study 26 out of 31 treated patients were evaluable for response to treatment. Two patients showed partial remission and 14 patients had stable disease in week 16. One patient experienced partial remission for at least 8 months. Nine patients had durable stable disease of 24 weeks or longer. Clinical benefit was obtained in 42% (11/26) patients. The median overall survival achieved was 30 months and the 2 year survival was 57%. Patients receiving extended treatment showed a significantly longer 2 year survival rate than discontinued patients (79% vs. 30%; p=0.0083).

Conclusion:
The treatment with the antibody cG250 in combination with the cytokines IL-2 or IFN α-2a showed clinical meaningful tumor responses and disease stabilizations and are of clinical benefit for this metastatic ccRCC patient population. The long term overall survival data is encouraging and warrants further investigation in controlled randomized studies.

* Temporary name while under development

AUA Meeting Anaheim, May 19 – 23, 2007

UPDATE OF SURVIVAL DATA FOR TWO PHASE II STUDIES WITH MONOCLONAL ANTIBODY CG250 (RENCAREX®*) IN COMBINATION WITH IL-2 OR IFNα-2A IN METASTATIC RENAL CELL CARCINOMA PATIENTS

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[1] Wilex AG, Munich, Germany, [2] Department of Hematology/Oncolog, Johannes-Gutenberg-Universität Mainz, Germany, [3] Department of Urology, Philipps-University-Marburg, Germany, [4] Onkologische Schwerpunktpraxis, Berlin, Germany, [5] Department of Urology, University Medical Center Nijmegen, Netherlands, [6] Department of Urology, Klinikum Großhadern, Ludwig-Maximilians-University, Munich, Germany, [7] Department of Urology, Klinikum Großhadern, Ludwig-Maximilians-University, Munich, Germany

WILEX
Focused Cancer Therapies

Introduction

cG250 (Rencarex®) is an IgG1 kappa light-chain chimeric monoclonal antibody that binds to carbonic anhydrase IX (G250 antigen), a cell-surface antigen found on 95% of cells in clear cell renal cell carcinoma (RCC). The reactivity of cG250 with normal tissues is restricted to the gastric epithelium and the biliary ducts in the liver, astrocytes in the brain and to the spinal cord. Besides efficient bio-localization in RCC, it has been shown that cG250 can induce NK cells to kill tumor cells in vitro via antibody dependent cellular cytotoxicity (ADCC).

A phase II study with weekly administrations over 12 weeks in 36 metastatic RCC patients has shown that cG250 antibody alone is safe when given at a dose of 50 mg per week. Clinical benefit was seen in 9 of 32 evaluated patients (28%). Median survival time was 15 months.

Two multi-center, open-label, prospective, single-arm phase I/II trials have been performed in combination with cytokines. 20 mg of cG250 was combined weekly with low dose (LD) interleukin 2 (IL-2) or with LD interferon (IFN) α-2a respectively evaluating the safety and efficacy in patients with metastatic ccRCC.

This abstract provides updated survival and clinical data of these combination studies of LD cytokines with the monoclonal antibody cG250.

Study design

- Two Phase II, prospective, non-randomized, open-label, single arm, multi-center studies in patients with metastatic ccRCC.
- In the IL-2 combination trial 35 patients, in the IFNα-combination trial 31 patients were enrolled for 12 weeks of treatment.
- At week 16 patients were evaluated for response and stratified into 1) the extended treatment group for an additional 6 weeks of treatment (included non-response patients if further treatment considered clinically useful) or, 2) the progressive group with no further treatment.

Dosing

	cG250 i.v.	IFN-α s.c.	IL-2 s.c.
Week 1	None	Day 1-3-5 (each 3 MIU)	1.8 MIU daily, except for biweekly pulses of 5.4 MIU/day for 3 cosecutive days)
Week 2-12	Day 1: 20 mg	Day 1-3-5 (each 3 MIU)	
For all patients with extension of treatment			
Week 17-22	Day 1: 20 mg	Day 1-3-5 (each 3 MIU)	1.8 MIU daily

Patient selection

MAIN INCLUSION CRITERIA

- Stage IV clear cell RCC, nephrectomized for primary tumor
- In progression at study entry
- Bi-dimensionally measurable disease with individual lesions ≤ 5 cm in diameter with at least one lesion of ≥ 1 cm
- Karnofsky performance status ≥ 80 %

MAIN EXCLUSION CRITERIA

- Known standard therapy that is potentially curative or definitely capable of extending life expectancy
- Any CNS metastases
- Patients with bone metastases only
- Lymphangiosis carcinomatosa
- Pre-exposure to murine/chimeric antibody therapy

Objectives

- Primary objectives: tumor response, toxicity
- Secondary objectives: immunogenicity (human anti-chimeric antibodies - HACA), biological activity (antibody dependent cellular cytotoxicity - ADCC), time to progression, overall survival

Results

TUMOR RESPONSE

For tumor response assessment, CT scans at baseline, and weeks 16 and 22 were evaluated. Further CT scans at three monthly intervals after end of treatment were evaluated in cases of clinical response (stable disease or objective response). All images were evaluated by an independent radiologist. In both studies patients had either low or intermediate risk based on modified Motzer criteria.

In the IL-2 combination study 30 patients were evaluable for response to treatment; in week 16 one patient showed a partial response (PR), 11 patients stable disease (SD). One patient experienced a partial remission for at least 95 weeks. 6 patients had long durable disease stabilization (≥ 24 weeks). Clinical benefit, defined as the sum of patients with a response and the sum of patients with SD ≥ 24 weeks, was obtained in 7 patients (23%).

In the IFNα-combination study 26 patients were evaluable for response to treatment; 2 patients showed a PR and 14 patients SD in week 16. One patient experienced a partial remission for at least 8 months. 9 patients had long durable disease stabilization (≥ 24 weeks). Clinical benefit, defined as the sum of patients with a response and the sum of patients with SD ≥ 24 weeks, was obtained in 11 patients (42%).

SURVIVAL

The IL-2 combination trial data show a median survival of 22 months with 45% of the 30 evaluable patients still alive after 2 years. (Figure1).

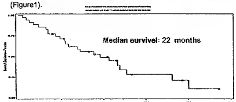

Figure 1

The extended treatment group receiving an additional 8 weeks of treatment showed a median survival of 41 months compared with 13 months in the non-response group. Patients receiving extended treatment with WX-G250 showed a significantly longer survival rate than the non-response patients (55% versus 25%; p=0.0062) (Figure 2).

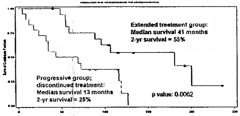

Figure 2

The overall median survival for patients in the IFNα-combination study was 30 months for the 31 patients treated with WX-G250 (Figure 3) with 57% of patients still alive after 2 years.

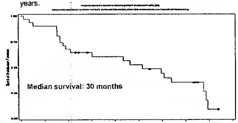

Figure 3

The response group receiving extended treatment showed a median survival of 45 months compared with 10 months in the non-response group. Patients receiving extended treatment with WX-G250 showed a significantly longer survival rate than the non-response patients (79% versus 30%; p=0.0083) (Figure 4).

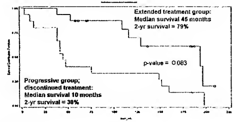

Figure 4

Results of phase II studies

Study	No. of Patients Evaluated	Response Rate (%)	Clinical Benefit Rate (%)	Median Survival (months)	2-Year Survival All Patients
WX-G250 monotherapy	36	3.1	28	15	41%
WX-G250 & IL-2	35	3.3	23	22	45%
WX-G250 & IFN-α	31	3.2	42	30	57%

Conclusion

- cG250 in combination with IL-2 and IFN-α showed an encouraging extension of survival with a median overall survival of 22 and 30 months respectively
- Weekly administrations of 20 mg cG250 combined with low dose cytokines were safe and very well tolerated.
- The demonstrated anti-tumor activity associated with a good clinical benefit rate and a prolonged median survival in this difficult-to-treat group of progressive metastatic renal cell carcinoma patients warrant further investigation

Phase III Trial Underway

A new clinical study has started to evaluate cG250 versus placebo in the adjuvant setting in patients at high risk of recurrence after recent nephrectomy.

For more information please refer the NCI homepage www.cancer.org (study code: Wilex-WX-2003-07-HR) or to clinical.trials@wilex.com.

The IND number of this phase III study is BB-IND11346

www.wilex.com

ASCO, CHICAGO, 01.-05. JUNE 2007

UPDATE OF SURVIVAL DATA FOR TWO PHASE II STUDIES WITH MONOCLONAL ANTIBODY CG250 (RENCAREX®*) IN COMBINATION WITH IL-2 OR IFNα-2A IN METASTATIC RENAL CELL CARCINOMA PATIENTS

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[6] Department of Urology, Klinikum Großhadern, Ludwig-Maximillians-University, Munich, Germany
[7] Department of Urology, Klinikum Großhadern, Ludwig-Maximillians-University, Munich, Germany

Background:
cG250 is a chimeric monoclonal antibody of the IgG1 subtype that binds to the cell surface antigen of carboxyanhydrase IX/MN antigen found on 95% of clear cell Renal Cell Cancer Cells (ccRCC) cells but not on normal kidney tissue.
Two multi-center, open-label, prospective, single-arm phase I/II trials have been performed. cG250 was combined with low dose (LD) Interleukin 2 (IL-2) or with LD Interferon (IFN) α-2a evaluating the safety and efficacy in patients with metastatic ccRCC.
This abstract provides updated survival and clinical data of these combination studies with cG250.

Methods:
Patients with stage IV ccRCC, nephrectomized for the primary tumor, and in progression at study entry were included in the study. In both trials cG250 was administered intravenously weekly from week 2 to 12. In addition, patients were treated with low dose cytokine treatment from week 1 to 12. At week 16 patients evaluated for clinical response were stratified into 2 groups: a) clinical responders into the extended treatment group to receive treatment for an additional 6 weeks, or b) clinical non-responders into the discontinued group.

Results:
In the combination study with IL-2 35 patients were treated. One out of 30 evaluable patients showed partial remission for at least 8 months. 11 patients had stable disease in week 16; of which 6 patients had durable stable disease of 24 weeks or longer. Clinical benefit, defined as the sum of complete or partial responses and patients with stable disease of ≥ 24 weeks, was obtained in 23% (7/30) patients. Newest data showed a median overall survival of 22 months and a 2 year survival of 45%. Patients receiving extended treatment showed a longer 2 year survival rate than discontinued patients (55% vs. 25%; p=0.0062)
For the IFN combination study 26 out of 31 treated patients were evaluable for response to treatment. Two patients showed partial remission and 14 patients had stable disease in week 16. One patient experienced partial remission for at least 8 months. Nine patients had durable stable disease of 24 weeks or longer. Clinical benefit was obtained in 42% (11/26) patients. The median overall survival achieved was 30 months and the 2 year survival was 57%. Patients receiving extended treatment showed a significantly longer 2 year survival rate than discontinued patients (79% vs. 30%; p=0.0083).

Conclusion:
The treatment with the antibody cG250 in combination with the cytokines IL-2 or IFN α-2a showed clinical meaningful tumor responses and disease stabilizations and are of clinical benefit for this metastatic ccRCC patient population. The long term overall survival data is encouraging and warrants further investigation in controlled randomized studies.

* Temporary name while under development

Kidney Cancer Symposium in Chicago (12.-13. Oktober 2007).

REVIEW OF THE MONOCLONAL ANTIBODY cG250 (RENCAREX®*) ALONE OR IN COMBINATION WITH IL-2 OR IFNα-2a IN METASTATIC RENAL CELL CARCINOMA PATIENTS

N. Neville[1], P. Kloepfer[1], P. Bevan[1], C. Mala[1], J Beck[2], R. Hofmann[3], M. Kindler[4], A. Knuth[5], P. Mulders[6], M. Siebels[7], G. Stoter[8], R. Oberneder[7]

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Background:
cG250 is a chimeric monoclonal antibody (IgG1) that binds to the cell surface antigen carboxyanhydrase CA-IX expressed on 95% of clear cell Renal Cell Cancer (ccRCC) cells but not on normal kidney tissue, and elicits antibody dependent cellular cytotoxicity (ADCC). Three multi-center, open-label, prospective, single-arm phase I/II trials were completed of cG250 monotherapy or in combination with low dose (LD) Interleukin-2 (IL-2) or Interferon (IFN)α-2a. Here we provide updated survival and clinical data of these three studies with cG250.

Methods:
Patients with stage IV ccRCC, nephrectomized for the primary tumor, and in progression at study entry were included. In the monotherapy study cG250 was given intravenously (i.v) at a dose of 50 mg per week (week 1-12). In the combination trials 20 mg of cG250 weekly (week 2-12) was combined with LD subcutaneous injections (s.c) of IL-2; (1.8 – 5.4 MIU/day) or with LD s.c. IFNα-2a (3 MIU, 3 times per week). LD cytokines were administered from week 1 to 12. At week 16 patients were evaluated for clinical response and stratified into 2 groups: 1) the extended treatment group, including clinical responders (and non-responsive patients if further treatment was considered clinically useful by the investigator). These patients were treated for an additional 8 weeks in the monotherapy trial, or 6 weeks in the combination trials or, 2) the progressive group, which received no further treatment.

Results:
In the **monotherapy study** 32 of 36 included patients were evaluable for response to treatment, eleven of whom showed stable disease (SD) in week 16. One patient experienced a minor response in week 44 and another patient a complete response (CR) in week 38. Clinical benefit defined as a complete or partial response or SD lasting 24 weeks or longer, was observed in 28% (9/28) of the patients. The median survival was 15 months, and the 2 year survival was 41% of the evaluable patients. Patients receiving extended treatment with cG250 for a further 8 weeks showed a median survival of 39 months, compared to 10 months in the discontinued group. 70% of patients in the extended group were still alive after 2 years, whereas only 26% of the discontinued group survived longer than 2 years (p=0.01).

In the **combination study with IL-2** 35 patients were treated. One out of the 30 evaluable patients showed partial remission for at least 8 months. Eleven patients had stable disease in week 16, six of whom had durable stable disease lasting 24 weeks or longer. Clinical benefit was observed in 23% (7/30) patients. A median overall survival of 22 months and a 2 year survival of 45% were noted. Patients receiving extended treatment showed a longer 2 year survival than discontinued patients (55% vs. 25%; p=0.0062).

For the **IFN combination study** 26 out of 31 treated patients were evaluable for response to treatment. Two patients showed partial remission and 14 patients had stable disease in week 16. One patient experienced partial remission for at least 8 months. Nine patients had durable stable disease of 24 weeks or longer. Clinical benefit was obtained in 42% (11/26) patients. The median overall survival achieved was 30 months and the 2 year survival was 57%. Patients receiving extended treatment showed a significantly longer 2 year survival rate than discontinued patients (79% vs. 30%; p=0.0083).

Conclusion:
Short-term treatment with the antibody cG250 either as monotherapy or in combination with the cytokines IL-2 or IFN α-2a led to clinically meaningful tumor disease stabilization and demonstrated clinical benefit in this pretreated, progressive metastatic ccRCC patient population. The long term overall survival data are encouraging and warrant further investigation in controlled randomized studies.

* Temporary name while under development

KCS, Chicago, October 12.-13. 2007

Appendix A
U.S. Serial Number 10/5[illegible]38

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REVIEW OF THE MONOCLONAL ANTIBODY cG250 (RENCAREX®) ALONE OR IN COMBINATION WITH IL-2 OR IFNα-2A IN METASTATIC RENAL CELL CARCINOMA PATIENTS

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Introduction

cG250 (Rencarex®) is an IgG1 kappa light-chain chimeric monoclonal antibody that binds to carbonic anhydrase IX (CAIX), a cell-surface antigen found on 95% of cells in clear cell renal cell carcinoma (ccRCC).

The reactivity of cG250 with normal tissues is restricted to the gastric epithelium and the biliary ducts in the liver, astrocytes in the brain and to the spinal cord. Besides efficient bio-localization in ccRCC, it has been shown that cG250 can induce natural killer (NK) cells to kill tumor cells in vitro via antibody dependent cellular cytotoxicity (ADCC).

Three multi-center, open-label, prospective, single-arm phase I/II trials were completed. cG250 was given either as monotherapy or in combination with low dose (LD) Interleukin-2 (IL-2) or Interferon (IFN)α-2a.

This poster reports updated survival and clinical data from these three studies with c G250.

Study design

- Three Phase I/II, prospective, non-randomized, open-label, single arm, multi-center studies in patients with metastatic ccRCC.
- In the monotherapy 36 patients were included for treatment, in the IL-2 combination trial 36 patients (1 pat. was never treated), and in the IFNα-combination trial 32 patients for 12 weeks of treatment (also here 1 patient was never treated).
- At week 16 and 22 patients were evaluated for response and stratified into
  1) the extended treatment group for an additional 8 weeks of treatment in the monotherapy study, or 6 weeks in the combination trials (included non-responsive patients if further treatment was considered clinically useful) or,
  2) the progressive group with no further treatment.

Treatment

	Mono cG250 i.v.	Combo cG250 i.v.	IFN-α s.c.	IL-2 s.c.
Week 1	d1q8: 50 mg	None	d1-3-5 (each 3 MIU)	1.8 MIU daily, and biweekly pulses of 5.4 MIU/day for 3 consecutive days
Week 2-12	d1q8: 50 mg	d8q8: 20 mg	Day 1-3-5 (each 3 MIU)	
	For all patients with extension of treatment:			
	Wk 17-24:	Wk 17-22	Wk 17-22	Wk 17-22

Patient selection

MAIN INCLUSION CRITERIA

- Stage IV ccRCC, nephrectomized for primary tumor
- Progressive disease at study entry
- Bi-dimensionally measurable disease with individual lesions ≤ 5 cm in diameter with at least one lesion of ≥ 1 cm
- Karnofsky performance status ≥ 80 %

MAIN EXCLUSION CRITERIA

- Known standard therapy that is potentially curative or definitely capable of extending life expectancy
- Any CNS metastases
- Patients with bone metastases only
- Lymphangiosis carcinomatosa
- Pre-exposure to murine/chimeric antibody therapy

Objectives

- Primary objectives: tumor response, toxicity
- Secondary objectives: immunogenicity (human anti-chimeric antibodies - HACA), biological activity (antibody dependent cellular cytotoxicity - ADCC), time to progression, overall survival

Results

TUMOR RESPONSE

CT scans were evaluated for tumor response at baseline, and in weeks 16 and 22. In the presence of clinical response CT scans were evaluated at three month intervals after the end of treatment by an independent radiologist. In all studies patients had either low or intermediate risk based on modified Motzer criteria.

In the monotherapy trial 32 of 36 patients were evaluated for response to treatment, eleven of which showed stable disease (SD) in week 16. One patient experienced a minor response in week 44 and another patient a complete response (CR) in week 38. Clinical benefit, defined as CR + PR + [SD ≥ 24 weeks], was obtained in 28% (9/28) of the patients.

In the IL-2 combination study 30 of 35 patients were evaluable. In week 16 one patient showed a partial response (PR), and 11 patients showed stable disease (SD). One patient experienced a partial remission for at least 95 weeks and 6 patients had durable disease stabilization lasting 24 weeks or longer. Clinical benefit was obtained in 23% (7/30) of the patients.

In the IFNα-combination study 28 of 31 patients were evaluable for response to treatment. Two patients showed a PR and 14 patients SD in week 16. One patient experienced a partial remission for at least 8 months and 9 patients had long durable disease stabilization (≥ 24 weeks). Clinical benefit was obtained in 42% (11/26) of the patients.

Survival

The monotherapy trial showed a median overall survival of 15 months with 41% of the 32 evaluable patients still alive after 2 years. (Figure1).

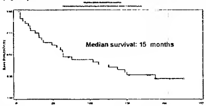

Figure 1

The extended treatment group (additional 8 weeks of treatment) showed a median survival of 30 months, compared to 10 months in the discontinued group. Patients receiving extended treatment with cG250 showed a significantly longer survival rate than the non-response patients (70% versus 26%; p=0.01). (Figure 2)

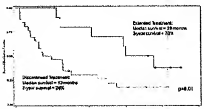

Figure 2

The IL-2 combination trial data show a median overall survival of 22 months with 45% of the 30 evaluable patients still alive after 2 years. (Figure 3).

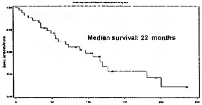

Figure 3

The extended treatment group (additional 8 weeks of treatment) showed a median survival of 41 months, compared with 13 months in the non-response group. Patients receiving extended treatment with WX-G250 showed a significantly longer survival rate than the non-response patients (55% versus 25%, p=0.0062). (Figure 4).

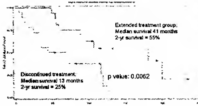

Figure 4

The overall median survival for patients in the IFNα-combination study was 30 months for the 31 patients treated with WX-G250 (Figure 5) with 57% of patients still alive after 2 years.

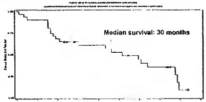

Figure 5

The patients receiving extended treatment showed a median survival of 45 months compared with 10 months in the non-extended group. Patients receiving extended treatment with cG250 showed a significantly longer survival rate than the non-response patients (79% versus 30%, p=0.0083) (Figure 6)

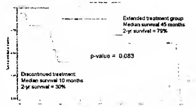

Figure 6

Results of phase II studies

Study	No. of Patients	Response Rate*	Clinical Benefit Rate (%)	Median Survival Rate (mo)	2-Year Survival Rate All Patients
WX-G250 monotherapy	36	3.1	28	15	41%
WX-G250 IL-2	36	3.3	23	22	45%
WX-G250 &IFN	32	3.8	42	30	57%

*based on evaluated patients

Conclusion

- cG250 both alone and in combination with IL-2 and IFN-α showed an encouraging extension of survival with a median overall survival of 15, 22 and 30 months respectively.
- Weekly administrations of 50mg or 20 mg cG250 combined with low dose cytokines were safe and very well tolerated.
- The demonstrated anti-tumor activity associated with a good clinical benefit rate and a prolonged median survival in this difficult-to-treat group of progressive metastatic renal cell carcinoma patients warrant further investigation.

Phase III Trial Underway

An international, randomized, placebo-controlled phase III clinical study is evaluating cG250 vs. placebo in the adjuvant setting in patients at high risk of recurrence after recent nephrectomy.

For more information please refer the NCI homepage www.cancer.org (study code: Wilex-WX-2003-07-HR) or to clinical.trials@wilex.com.

Study IND number: BB-IND11346

www.wilex.com